PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/00 — A2

(11) International Publication Number: **WO 99/02142**

(43) International Publication Date: 21 January 1999 (21.01.99)

(21) International Application Number: PCT/EP98/04971

(22) International Filing Date: 7 July 1998 (07.07.98)

(30) Priority Data:
9714675.7 11 July 1997 (11.07.97) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CUMMINGS, Paul, John [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). TULLOCH, Ian, Frederic [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL COMPOSITION

(57) Abstract

A pharmaceutical composition comprising an SSRI in quick–release form and a β–blocker in sustained–release form.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

NOVEL COMPOSITION

This invention is concerned with novel formulations of selective serotonin re-uptake inhibitors (SSRI's). In particular the present invention provides formulations that potentiate the therapeutic activity of an SSRI, and especially that improve the onset of the therapeutic effect.

Artigas *et al* (Arch. Gen Psychiatry, Vol. 51, pp 248-251, Mar. 1994) have reported that administration of pindolol (2.5 mg. three times a day) during treatment with the SSRI paroxetine (20 mg once per day) relieved depression in patients previously showing no benefit from treatment with paroxetine.

Subsequently, it has been proposed in EP-A-0714663 that the effect of the SSRIs citaloprolam, fluvoxamine and paroxetine can be potentiated by co-administration in certain combinations with *inter alia* pindolol, penbutolol, propranol and tertatolol and other compounds known to be serotonin IA receptor antagonists, but excluding the combination paroxetine-pindolol.

A problem with any co-administration regime is ensuring patient compliance, particularly in a regime such as proposed by Artigas which involves taking medication on three occasions during the day (assuming that the paroxetine dose and the first pindolol dose are taken simultaneously).

The present invention aims to overcome the problems associated with co-administration of SSRIs and potentiating compounds.

In its broadest aspect, the present invention provides an SSRI composition comprising an SSRI in quick release form and a β-blocker in sustained release form. The composition is conveniently in tablet or capsule form.

Typical SSRIs used in this invention are paroxetine, fluvoxamine, citalopram and sertraline. Preferably the SSRI is paroxetine. The co-administered β-blocker is preferably pindolol.

The preferred combination of SSRI and β-blocker is paroxetine and pindolol. Preferably the tablet or capsule contains 20 mg of paroxetine in an immediate release form and 7.5 mg of pindolol in a sustained release form.

Typically the sustained release form of the β-blocker is provided to release the equivalent of a three times daily dose continuously over a period of 12-16 hours. Alternatively, the dose may be released in three spaced tranches.

When the SSRI is combined with a β-blocker in a continuous release formulation, then the composition of the invention is preferably presented as a bi-layer tablet in which one layer contains an SSRI in a conventional quick release formulation and the other layer contains a β-blocker in a sustained release formulation.

The sustained release may be provided by formulating the β-blocker with any conventional sustained release excipient or blend of excipients that does not interact with the β-blocker or the SSRI.

Suitably, the sustained release properties are provided by incorporating the β-blocker in an excipient which swells in gastric juice, typically forming a gel which dissolves and/or is abraded as the tablet passes through the patient's gut, releasing the active ingredient. The rate of release may be controlled in a conventional manner by varying the molecular weight of the excipient and/or co-formulating a primary excipient with materials that dissolve or disintegrate at a different rate than the primary excipient, to form micropores in a swollen or gelled primary excipient.

Suitable primary excipients may be selected from swellable binders such as methyl cellulose for example as sold under the trade mark Methocel K4M and E5, ethyl cellulose, polyacrylic acid for example as sold under the trade mark Carbopol 974P, polyacrylic esters for example as sold under the trade mark Eudragit L30D and RS30D, xanthan gum, and starch.

The release profile of the primary excipient may be varied by incorporating fillers and disintegrants such as lactose especially lactose monohydrate, microcrystalline cellulose for example as sold under the trade mark Avicel pH102, calcium sulphate, dicalcium phosphate for example as sold under the trade mark Encompress, polyvinyl pyrrolidone for example as sold under the trade mark Povidone 30, hydrogenated vegetable oils for example as sold under the trade mark Lubritab.

Conventional tableting excipients may also be included to assist tablet manufacture, for example as die lubricants etc., such as magnesium stearate, glyceryl behenate for example as sold under the trade mark Compritol 888.

Alternatively, the composition may be a capsule presentation comprising coated pellets of a β-blocker, which is a mixture of coated pellets having different dissolution times, dispersed in a powder formulation of an SSRI, all contained within a soluble capsule.

Suitably, the coating of the pellets of the β-blocker is a material that is resistant to gastric juices but dissolves in the gut, for example. Dissolution times may be varied by varying the coating thickness. Preferably the coated pellets are mixed so as to provide a substantially continuous release of pindolol, but if desired the pellets may be a mixture of three coating thicknesses so that pindolol is released in three tranches over a the desired dosage period such as 12-14 hours. A powdered formulation of the SSRI be be made by blending the SSRI with conventional excipients. Soluble capsules to contain the combination of active ingredients may be conventionally made from gelatine.

Typical sustained release formulations of the above described hydrophilic matrix type and enteric coating type that may be used in this invention are disclosed in standard textbooks on the subject.

We have found that a suitable release profile for clinical use is obtained when the sustained release β-blocker formulation has a release profile measured *in vitro* in acid/buffer which has a dissolution time $T_{50\%}$ of 1.73 hours, a $T_{90\%}$ of 8.45 hours and a $T_{100\%}$ of 14 hours.

Accordingly, a preferred embodiment of the invention provides a formulation of an SSRI and a β-blocker in which the β-blocker is in a sustained release form having a release profile *in vitro* in which the $T_{50\%}$ is 1.73 hours $\pm$ 20%, the $T_{90\%}$ is 8.45 hours $\pm$ 20% and the $T_{100\%}$ is 14 hours $\pm$ 20%.

Preferably, the SSRI is paroxetine hydrochloride, most preferably at a dosage of 20 mg, and the β-blocker is pindolol, most preferably at a dosage of 7.5 mg.

The pindolol is typically used as the commercially available racemate. However, active isomers thereof may be used at a dosage adjusted for bioquivalence to a stated dose of the racemate.

Therapeutic uses of compositions of this invention, especially compositions of paroxetine hydrochloride and pindolol, include treatment of alcoholism, anxiety, depression, obsessive compulsive disorder (OCD), panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, premenstrual syndrome (PMS),

adolescent depression, trichotillomania, dysthymia and substance abuse; referred to herein as "the Disorders".

Accordingly, the present invention also provides

use of an SSRI and a sustained release form of a β-blocker for the manufacture of a tablet or capsule for the treatment or prophylaxis of the Disorders in humans and animals, and

a method for the treatment or prophylaxis of the Disorders, which comprises administering a tablet or capsule comprising an SSRI and a sustained release form of a β-blocker to a person or animal in need thereof.

In the use and method of the invention, the tablet or capsule is preferably a composition of this invention having the preferred values indicated above.

The invention is illustrated by the following Example:

Example 1

Bi-layer tablets of paroxetine and sustained release pindolol were manufactured as follows.

Pindolol Component

A sustained release form of pindolol based upon a hydrophilic matrix with a soluble filler/disintegrant to increase the porosity of the matrix once hydrated was prepared by high shear wet granulation of a mixture of :

pindolol base	7.5 parts by weight
methylcellulose (Methocel K4M)	35 parts by weight
lactose monohydrate	25 parts by weight
microcrystalline cellulose (Avicel pH102)	32 parts by weight

After drying and screening, 0.5 parts by weight of glyceryl behenate (Compritol 888) as a lubricant were incorporated by tumble blending.

Paroxetine Component

An immediate release formulation of paroxetine was prepared by blending 20 parts per weight of paroxetine hydrochloride and 80 parts per weight of conventional excipients.

Tableting

100 mg. amounts of the sustained release pindolol formulation were charged into tablet moulds in a rotary tableting platen at a first charging station. After a preliminary light pressing to locate the powdered formulation in the tablet mould, the platen was indexed to a second charging station where 152 mg. of the paroxetine formulation were introduced on top of the sustained release formulation. The two layer mixture in the tablet mould was then given a full press to prepare 252 mg. tablets containing 20 mg. paroxetine hydrochloride and 7.5 mg. pindolol in a sustained release base, each active component being in separate layers of a bi-layer tablet.

Claims

1. A pharmaceutical composition comprising an SSRI in quick-release form and a β-blocker in sustained-release form.

2. A pharmaceutical composition according to claim 1 which takes the form of a bi-layer tablet in which one layer contains the SSRI in a quick-release formulation and the other layer contains the β-blocker in a sustained-release formulation.

3. A pharmaceutical composition according to claim 1 which takes the form of a capsule which contains an admixture of a quick-release formulation of the SSRI and a sustained-release formulation of the β-blocker.

4. A pharmaceutical composition according to any one of claims 1 to 3 in which the β-blocker is in a sustained release form having a release profile *in vitro* in which the $T_{50\%}$ is 1.73 hours ± 20%, the $T_{90\%}$ is 8.45 hours ± 20% and the $T_{100\%}$ is 14 hours ± 20%.

5. A pharmaceutical composition according to any one of claims 1 to 4 in which the SSRI is paroxetine or a pharmaceutically acceptable derivative thereof.

6. A pharmaceutical composition according to claim 5 in which the paroxetine is in the form of the hydrochloride.

7. A pharmaceutical composition according to any one of claims 1 to 6 in which the β-blocker is pindolol.

8. A pharmaceutical composition according to claim 7 in which the pindolol is present as the racemate.

9. A pharmaceutical composition according to claim 8 which contains 20mg of paroxetine hydrochloride and 7.5mg of pindolol as the racemate.

10. A pharmaceutical composition according to claim 7 in which the pindolol is present as an active isomer.

11. A method of treatment of alcoholism, anxiety, depression, obsessive compulsive disorder (OCD), panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia,

anorexia, social phobia, premenstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse which comprises administering an effective or prophylactic amount of a pharmaceutical composition as defined in claim 1 according to any one of claims 1 to 10 to a sufferer in need thereof.

12. The use of a pharmaceutical composition as defined in claims 1 to 10 in the manufacture of a medicament for the treatment or prevention of alcoholism, anxiety, depression, obsessive compulsive disorder (OCD), panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, premenstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse.

13. A pharmaceutical composition as defined in claims 1 to 10 for use in the treatment or prevention of alcoholism, anxiety, depression, obsessive compulsive disorder (OCD), panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, premenstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse.